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ADA-HF: A pilot study of the safety and efficacy of acetazolamide in patients admitted to hospital with heart failure

Submission date
04/11/2022

Recruitment status
No longer recruiting

Registration date
09/02/2023

Overall study status
Completed

Last Edited
28/04/2026

Condition category
Circulatory System

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Heart failure (HF) is a chronic condition characterised by fluid retention - "venous congestion" - due to impaired heart pump function causing breathlessness and limb swelling. Uncontrolled fluid retention due to HF is a common reason for hospital admission. Treatment of venous congestion is with diuretics that increase the amount of salt - predominantly sodium and chloride - passed in the urine. This, in turn, increases the amount of water excreted and so a patient loses fluid - diuresis.

The problem
Resistance to diuretics is common and adequate diuresis may take many days. Furthermore, commonly used diuretics may cause low chloride levels (hypochloraemia) in the blood which is linked to a poor prognosis. At present there are few treatments available for diuretic resistance or hypochloraemia.

The solution
Acetazolamide is a drug that may cause diuresis and increase serum chloride levels. It works on a different portion of the kidney to more commonly used diuretics and may therefore have an additive value that can either overcome diuretic resistance or speed up diuresis, thus shortening hospital stays. Increasing serum chloride may reduce the risk of developing hypochloraemia or treat those with hypochloraemia which may improve outcome. The effect of acetazolamide on diuresis or chloride levels in patients with HF is unknown but potentially beneficial.

Who can participate?
Adults over 18 years, admitted to hospital with a primary diagnosis of peripheral oedema caused by heart failure and deemed by treating clinicians to require treatment with intravenous diuretic

What does the study involve?
To test the diuretic effect of acetazolamide we will randomise up to 50 patients admitted with HF at a single tertiary cardiology centre in Yorkshire to either acetazolamide plus standard diuretic treatment or standard care alone over a four-day period. We will measure urine volume,

weight loss, patient symptoms, clinical and echocardiographic signs of congestion (non-invasive ultrasound tests) and urine and blood salt levels including kidney function on a daily basis. Patients will continue to be seen by the on-call cardiology team and will continue under their care once the trial is over.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
The British National Formulary lists the common or very common side effects of acetazolamide to be: ataxia, depression, diarrhoea, dizziness, fatigue, flushing, irritability, headache, loss of appetite, nausea, vomiting, taste disturbance, parasthesiae, reduced libido, polyuria, and thirst. Notable uncommon side effects include: metabolic acidosis, electrolyte disturbances, blood disorders, skin rashes and symptoms consistent with renal calculi.
The early studies suggested that side effects such as drowsiness and paraesthesia are seen in 14-38% of patients with heart failure at doses >1000mg per day, although side-effects were less common at doses ≤500mg per day (5-10%). Modern day studies did not report any adverse events but it is not explicitly stated that this is due to the medication being well tolerated.

We judge the above side effects to be of low clinical risk to the patient however it is possible a patient experiencing any one of those side effects after starting acetazolamide may wish to end their participation. This, in itself, would be a useful endpoint. One of the many unknowns about acetazolamide in contemporaneous studies is the tolerability used either in isolation or in conjunction with high dose loop diuretic.
There are potential risks to the patient from the combination of acetazolamide and high-dose loop diuretic treatment, however we are unable to estimate their expected frequency: 1) increased risk of hyponatraemia – as both medications increase urinary sodium excretion; 2) increased risk of symptomatic hypotension due to increased intravascular volume loss and 3) increased risk of renal dysfunction. Daily assessment of urine and serum electrolytes and the patient will detect any changes that might be associated with increased risk to the patient and these will be discussed with the patient regarding continuation. Again, this would be a useful endpoint in itself regarding tolerability of the combination of diuretics. Furthermore, worsening electrolyte abnormalities, symptomatic hypotension and worsening renal function would be expected in the standard care arm also.

Ultimately we would expect all treatment related adverse events to resolve upon withdrawal of the study treatment should the patient wish to do so or if the risk to the patient was felt too great to allow their continuation in the study.
Aside from the IMP, we anticipate no increased risk to either the patient or study staff by their participation in the study. All data will be recorded on paper CRFs and stored in a locked filing cabinet in an office with a locked door on NHS property accessible only via swipe-card. It will then be transferred to a password-protected Excel spreadsheet on a password protected NHS server behind an NHS firewall.

Where is the study run from?
Hull University Teaching Hospitals NHS Trust(UK)

When is the study starting and how long is it expected to run for?
November 2022 to July 2024

Who is funding the study?
British Heart Foundation (UK)

Who is the main contact?
Dr Joe Cuthbert, joe.cuthbert@hyms.ac.uk

Contact information

Type(s)
Principal investigator

Contact name
Dr Joseph Cuthbert

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Additional identifiers

Clinical Trials Information System (CTIS)
2022-001566-34

Integrated Research Application System (IRAS)
1005718

Protocol serial number
1988

Study information

Scientific Title
Acetazolamide as a chloride sparing Diuretic in patients Admitted with Heart Failure: a pilot and exploratory study (ADA-HF)

Acronym
ADA-HF

Study objectives
Primary objective:
To assess the effect of oral acetazolamide (250 mg BD) on
1. Diuresis measured in net fluid loss; and
2. Serum chloride concentrations when given alongside high dose intravenous furosemide compared to high dose furosemide alone in patients admitted to hospital with heart failure and severe oedema.

Secondary objective:
To assess the feasibility of performing a large scale trial of oral acetazolamide given alongside high dose intravenous furosemide in terms of number of eligble patients and the tolerability of the treatment.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 02/02/2023, East Midlands - Nottingham 2 Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, UK; +44 (0)207 104 8169, +44 (0)207 104 8278, +44 (0) 208 104 8051; nottingham2.rec@hra.nhs.uk), ref: 22/EM/0264

Study design
Interventional open label randomized parallel group controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Heart failure with severe venous congestion requiring hospital admission

Interventions
Patients will be randomised in 1:1 ratio using an online tool to receive oral acetazolamide 250mg twice per day plus usual care or usual care alone over a 4-day period. Usual care must involve intravenous furosemide infusion of 10mg per hour. Patients will be followed up for 4 days during their in-patient stay and for up 6 months after discharge.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Acetazolamide, furosemide

Primary outcome(s)
1. Difference in mean net fluid loss daily and over a 4 day period: total volume intake in millilitres (mL) – total volume passed as urine in mL
2. Difference in serum chloride concentrations measured at day 1 and day 4

Key secondary outcome(s))
1. Daily weight measured in kilograms at baseline, 24 hours, 48 hours, 72 hours, and 96 hours
2. Serum concentrations of sodium, bicarbonate, potassium, urea, and creatinine measured at baseline, 24 hours, 48 hours, 72 hours, and 96 hours
3. Urinary electrolyte concentrations measured twice during the trial over a 24 hour period

between 24 to 48 hours, and 72 to 96 hours
4. Clinical assessment of congestion measured by presence and severity of peripheral oedema, lung crackles, raised jugular venous pulse, or ascites at baseline, 24 hours, 48 hours, 72 hours, and 96 hours
5. Breathlessness measured using a Likert scale baseline, 24 hours, 48 hours, 72 hours, and 96 hours
6. Inferior vena cava diameter at baseline and 96 hours
7. Time to clinical euvolaemia measured by clinical assessment in the medical record at discharge
8. Time to discharge measured by difference between date of admission and date of discharge taken from the medical record
9. Number and percentage of adverse, serious adverse, and suspected unexpected serious adverse reactions between baseline and 6 months
10. Number and percentage of adverse, and serious adverse events between baseline and 6 months
11. Rate of recruitment to study measured by number of patients randomised as a percentage of the total number of patients screened measured after the last patient is randomised
12. Cause specific rate of drop out after randomisation measured after last patient last visit.
13. Cause specific hospitalisation and / or mortality after 30 and 180 days.

Completion date
31/07/2024

Eligibility

Key inclusion criteria
1. Aged >18 years of any gender and able to give informed consent (females of child bearing age must consent to and have a negative pregnancy test prior to randomisation)
2. Heart failure of any aetiology
3. Admitted to hospital with a primary diagnosis of peripheral oedema caused by heart failure and deemed by treating clinicians to require treatment with intravenous diuretic.
4. Patients are considered eligible as long as they are deemed to require standard of care (10mg per hour furosemide infusion).
5. Patients whose medications have been discontinued for other reasons >1 week previously may be considered eligible. These medications include; high dose aspirin (>500mg / day), methotrexate, lithium, Sando-K®, sodium bicarbonate, other sodium tablets, oral steroids, or sodium valproate.
6. Able to give informed written consent to participate in the trial.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit

100 years

Sex
All

Total final enrolment
46

Key exclusion criteria
1. Unable to give informed written consent
2. Allergy or contraindication to carbonic anhydrase inhibitors, or are taking another medication (other than loop diuretic) that has a diuretic effect such as bendroflumethiazide, metolazone or sodium-glucose linked transporter-2 inhibitors.
3. Patient thought to be at end-of-life
4. Concurrently taking thiazide (or thiazide-like) diuretic or sodium-glucose linked transporter-2 inhibitor
5. Concurrently taking high dose aspirin (>500 mg/day), methotrexate, lithium, or sodium valproate – risk of drug interactions with ACZ
6. Concurrently taking Sando-K®, oral sodium bicarbonate, or other sodium tablets – confounding electrolyte analysis
7. Concurrently taking oral steroids – confounding diuretic analysis
8. Peripheral oedema due to heart failure that has been triggered by an underlying illness such as severe anaemia (haemoglobin <8 g/DL) or concurrent severe infection (requiring intravenous antibiotics).
9. SBP <80 mmHg at randomisation
10. Serum sodium (severe hyponatraemia) <130 mmol/L at randomisation
11. Serum potassium (hypokalaemia) <3.5 mmol/L at randomisation
12. Serum chloride (severe hyperchloraemia) >110 mmol/L at randomisation
13. Severe renal dysfunction with an eGFR (estimate glomerular filtration rate) result of <30 ml /min calculated by the Cockcroft-Gault formula
14. Pregnant or intends to become pregnant whilst taking part in the trial

Date of first enrolment
01/01/2023

Date of final enrolment
31/01/2024

Locations

Countries of recruitment
United Kingdom

Study participating centre
Castle Hill Hospital
Castle Road
Cottingham
England
HU16 5JX

Study participating centre
Hull Royal Infirmary
Anlaby Road
Hull
England
HU3 2JZ

Sponsor information

Organisation
Hull University Teaching Hospitals NHS Trust

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation

Alternative Name(s)
The British Heart Foundation, the_bhf, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Anonymised data will be available to other researchers on reasonable request.
joe.cuthbert@hyms.ac.uk

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		27/04/2026	28/04/2026	Yes	No
HRA research summary			28/06/2023	No	No
Other publications	Rationale and design of the acetazolamide as a chloride sparing diuretic in patients admitted with heart failure (ADA-HF) trial	13/03/2025	27/03/2025	Yes	No
Participant information sheet	version 3	27/01/2023	04/12/2023	No	Yes
Protocol file	version 2	27/01/2023	04/12/2023	No	No